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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,534	ENSOLI, BARBARA	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *124-126,169-178 and 192* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-128 and 142-192.

Continuation of Disposition of Claims: Claims rejected are 62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-123,127,128,142-168 and 179-191.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 June 2006 has been entered.

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128, and 142-192 are pending. Claims 124-126, 169-178, and 192 are withdrawn from consideration. Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 are examined.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186 under 35 U.S.C. § 102(b) as being anticipated by Chang *et al.* is **maintained**. Applicant argues that the reference does not meet the limitation of being "pharmaceutically acceptable for administration to a human." Applicant's arguments have been fully considered but they are not persuasive. The claim limitation does not change the scope of the invention in that the active ingredients of the claimed product remain the same. Since the specification does not define any specific composition ingredients, in addition to the purified HIV Tat protein, that are required to be "pharmaceutically acceptable for administration to a human" and especially since the specification clearly states that the

inventor used the heparin affinity chromatography and the Tat purification protocol as described by Chang *et al.* (page 25, line 11), the instant claims are anticipated by Chang *et al.*

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 106, 107, 114, 119, 128, 142-150, 152, 153, 155-159, 161,162, 164-168, 179-183, 185, 186 and 189 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Heiman *et al.* is **maintained** for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-95, 97, 101-103, 105-111, 116, 117, 121, 122, 128, 142-168, 179-187, 190, and 191 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Vogel *et al.* is **maintained** for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 99, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Castignolles *et al.* is **maintained** for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 100, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Ramshaw *et al.* is **maintained** for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 112, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, 186, and 188 under 35

U.S.C. § 103(a) as obvious over Chang *et al.* in view of Livingston *et al.* is **maintained** for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 106, 107, 123, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang et al. in view of Barry et al. is **maintained** for the same reason as above.

New Grounds of Rejections

Claim Rejections - 35 USC § 112, 1st ¶, written description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

In the instant case, the claims are directed to a composition comprising biologically active HIV Tat protein. The limitation "fragments and mutants" encompasses all variants and structural or functional homologs as small as three amino acids. Thus, the claims are drawn to a genus of peptides that are defined only by function.

The full length Tat contains 101 amino acid residues. Each residue can be mutated to one of the other 19 naturally occurring amino acid. A Tat fragment can be from 3 to 100 amino acids long. The specification only provides description for 19

mutants at specific positions (p. 35, Table 2). There are still an inordinate number of fragment/mutant sequences that are not described in the specification. There is not even identification of any particular portion of the structure that must be conserved for the biological activity. Therefore, the 19 mutant species specifically disclosed are not representative of such a broad and highly variable genus.

While having written description of 19 mutant Tat proteins identified in the specification table, the specification is devoid of any other species that qualify for the functional characteristics claimed. A definition by function alone "does not suffice, to sufficiently describe a coding sequence" because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119F.3 at 1568, 43USPQ2d at 1406.

Therefore, claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 do not meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 112, 1st ¶, scope of enablement

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a composition comprising an isolated Tat protein, does not reasonably provide enablement for a Tat protein composition that is pharmaceutically acceptable for administration to a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors (MPEP §2164.01(a)).

Nature of the invention. The claims are drawn to a biologically active Tat protein-based HIV-vaccine. Furthermore, the specification clearly states on page 1 that the present invention refers to a prophylactic and/or therapeutic vaccine anti-HIV, anti-AIDS and against tumors and syndromes associated with HIV infection. Therefore, the instant claims, when read in light of the specification, would lead one skilled in the art to conclude that the instant invention is clearly directed towards HIV vaccines.

Breadth of the claims. The broad claims with the limitation "pharmaceutically acceptable for administration to a human" encompass vaccine compositions for preventing HIV in humans, and the limitation "fragment or mutant" encompasses a genus of inordinate number of HIV Tat species as small as three amino acids.

Working examples. A working example of monkeys is disclosed in the specification.

Guidance in the specification. The amount of direction is limited to a macaque model, wherein the administration of HIV Tat resulted in antigen-specific antibody response and CTL response (spec. example 5) and antigen-specific T-cell activation as determined by *in vitro* assays of PBMC samples (spec. example 4). This test is unreliable in detecting minority HIV-1 variants in the virus population of a patient. Resistant mutants may not persist at detectable levels in the absence of drug selection pressure (Martinez-Picado, 1998, pages 84, 85, and 87), which increases the complexity in extrapolating from *in vitro* to *in vivo* test results and even from one animal

model to humans. Even though the specification teaches the generation of natural immune response in monkeys, the disclosure does not relate to protection against any strain and/or clade of HIV-1 in humans.

State of the prior art. At the time the invention was made, a pharmaceutical HIV-vaccine comprising Tat protein, fragment or mutant is not considered routine in the art.

Predictability of the art. The state of the art of development of HIV vaccine is highly unpredictable, since HIV replicates rapidly with a high mutational frequency and creates diverse 'quasi-species', which are favored by the Darwinian selective pressures. Therefore, efforts to develop effective treatments and vaccines must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

Experimental HIV-1 infection *in vivo* and *in vitro* both suffer from the limitation that the *in vitro* amplification of HIV-1, which is required to prepare virus stocks for *in vitro* or *in vivo* infectivity experiments, impose a genetic selection that results in a spectrum of variants present in the clinical specimens used to establish the culture (Kusumi *et al.*, 1992; Meyerhans *et al.*, 1989). Because of these uncertainties, and even greater uncertainties related to the amount of virus transmitted, the site and cell type involved in initial replication, and the kinetics of virus dissemination, the ability of currently available *in vitro* or *in vivo* assays to reliably predict vaccine efficacy is questionable. Small trials in populations with low rates of infection and minimally sized

placebo control groups do not have sufficient statistical power to confirm or refute vaccine efficacy.

A natural immune response, consisting of antibody response and viral-specific $CD8^+$ cellular response as measured in the instant application, is not effective because HIV has evolved a number of evasion strategies: selection for genetic variants that are antigenic escapes variants; inherent resistance to antibody-mediated neutralization; down regulation of major histocompatibility class I molecules from the surface of infected cells by Nef; and destruction of viral-specific $CD4^+$ T helper cells. It is well established in the art that $CD8^+$ cellular responses, or cytotoxic T lymphocyte (CTL) responses select for viral escape variants that are resistant to immune recognition, but the fate of these escape mutants after transmission to new hosts is unclear. If CTL escape mutations can be reserved after transmission of HIV, HIV escape variants might be propagated in populations. Over time, epitopes targeted by CTL-based vaccines could be lost from circulating virus strains, rendering vaccines that are based on single or consensus strains ineffective. The main problem with HIV vaccines is that there has not been a solution to overcome the enormous sequence heterogeneity of HIV-1 (see Altman *et al.*, 2004; Desrosiers, 2004; Friedrich *et al.*, 2004; and Leslie *et al.*, 2004).

Furthermore, it is known for proteins, for example, that even a single amino acid mutation can destroy the functional activity of the biomolecule in many instances, albeit not in all cases. Viral transcription factor Tat is a small nuclear protein containing a large number of basic amino acids. The *tat* gene consists of two exons but only the first encoding 72-amino acid polypeptide is necessary for protein activity. Since the second

exon is poorly conservative the total number of amino acids among Tat proteins from different strains of HIV-1 varies from 86 to 130. The effects of mutation or truncation into smaller fragments are largely unpredictable as to which ones have a significant effect versus not, especially the fragments or mutants without the transduction domain (RKKRRQRRR). Therefore, the recitation of "fragment or mutant" in claim 62 results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement. See Naryshkin *et al.* (1998) and Campbell *et al.* (2005) for example.

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, a pharmaceutical HIV-vaccine comprising an isolated Tat protein is not considered routine in the art and, without sufficient guidance to its clinical efficacy, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Remarks

No claim is allowable.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP §714.02 and §2163.06.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
24 October 2006

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